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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,062	03/09/2005	Takayuki Furuishi	267344US0PCT	4749

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OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
GRAZIER, NYEEMAH	
ART UNIT	**PAPER NUMBER**
1626	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	03/09/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 03/09/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@oblon.com
oblonpat@oblon.com
jgardner@oblon.com

Office Action Summary	Application No.	Applicant(s)	
	10/527,062	FURUISHI ET AL.	
	Examiner	Art Unit	
	Nyeemah Grazier	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 8-12* is/are rejected.

7)☒ Claim(s) *5-7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/9/05,2/13/06,5/18/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

FIRST ACTION ON THE MERITS

I. ACTION SUMMARY

Claims 1-12 are currently pending.

II. PRIORITY

This application is a 371 of PCT/JP03/11420, filed September 8, 2003. Applicant's claim under 35 USC 119 (a-d) to foreign application JAPAN 2002-265276, filed September 11, 2002 is acknowledged.

III. INFORMATION DISCLOSURE STATEMENT

The information disclosure statements (IDS) submitted on March 9, 2005, February 13, 2006, and May 18, 2005 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

IV. REJECTION(S)

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compounds of formula (I), the disclosure is not enabling foe the method of treating *any and all pathological conditions affected or induced by activation of angiotensin-converting enzyme (ACE).*

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The relevant factors to be considered in determining whether a disclosure meets the enablement

requirement of 35 U.S.C. 112, first paragraph have been set forth in *In re* Wands. See *In re* Wands, 8 USPQ.2d 1400 (1988). The factors are as follows:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The relative factors are factors 3, 4, and 5 and are discussed separately below.

The Predictability or Lack Thereof in the Art

The present invention teaches a method of using the products of Formula (I) to treat ACE related conditions by administering the drug *percutaneously,* thereby avoiding potential digestive problems that tend to accompany oral administration of the drug. See, Specification, pp. 1-4. By the applicant's own admission, enalapril and enalaprilat "have not been successfully formed into percutaneous preparations." Specification at p. 2. Therefore, there is a lack of predictability in the art.

The Specification also teaches that enalapril is widely used as a peroral agent in clinical settings as an antihypertensive pharmaceutical agent. "Enalapril is a prodrug produced following oral administration, it is bioactivated by hydrolysis of the ethyl ester to enalaprilat, which is the active angiotensin converting enzyme inhibitor." IP, Dominic P., et al. "Enalapril Maleate," Analytical Profiles of Drug Substances, vol. 16, pp. 207-243, 209 (1987). The difference between the instant invention and enalapril and enalaprilat is that in the instant formula (I) the carboxylate group at the 2 position on the pyrrolyl ring is particularly substituted by "R1."

> wherein R^1 represents a hydroxy-lower alkyl group, a lower alkoxy-lower alkyl group, or a lower alkoxy-lower alkoxy-lower alkyl group or a pharmaceutically acceptable salt thereof.

There is no pharmacological data relative to the instant invention of Formula (I).

The Amount of Direction or Guidance Present

The amount of guidance present in the specification is relative to the production of medicated patches comprising the compounds of Formula (I), skin permeability test, and the use of enalapril and enalaprilat as antihypertensive agents. There is no guidance in the specification pertaining to the method of using the compounds of formula (I) as a medicament.

Also, enalapril and enalaprilat "have not been successfully formed into percutaneous preparations." Specification at p. 2. Therefore, there is insufficient guidance regarding the success of the drug when administered percutaneously.

The Presence of Working Examples

There is no pharmacological data relative to the instant invention of Formula (I). The amount of guidance present in the specification is relative to the production of medicated patches comprising the compounds of Formula (I), skin permeability test, and the use of enalapril and enalaprilat as antihypertensive agents. There is no guidance in the specification pertaining to the method of using the compounds of formula (I) as a medicament.

Claim Rejections - 35 USC §§ 112 and 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8-10 provides for the use of "producing a drug," but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 3 and 4 are also rejected because (1) claim 3 recites a "drug comprising" but only mentions one element, verily, the compound recited in claim 1 or 2; and (2) claim 4 recites a "preparation" without reciting steps of the preparation.

Claims 8-10 are also rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) that forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Graham v. John Deere Co. set forth the factual inquiries necessary to determine obviousness under 35 U.S.C. §103(a). *See Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Specifically, the analysis must employ the following factual inquiries:

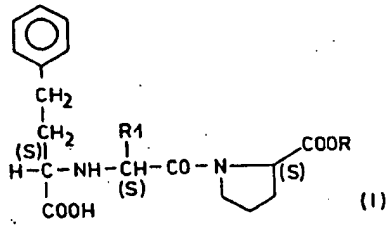
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1 and 2 are rejected under 35 U.S.C. § 103(a) as being obvious over *HU 196834 (abstract)* in view of Green, et al., Protective Groups in Organic Chemistry, Chapter 5: Protection for the Carboxyl Group, 3rd Ed., p. 382, 388, and 390 (1999).

The Scope and Content of the Prior Art (MPEP §2141.01)

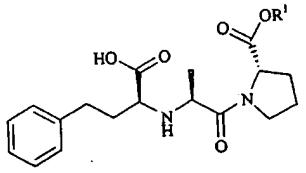
The prior art teaches the following formula wherein "R" is a protective group. See, Abstract, HU 196834.



(I)

The Difference Between the Prior Art and the Claims (MPEP §2141.02)

The difference between the instant invention and the prior art of record is in scope. The instant invention is drawn to the compound of Formula (I) wherein R1 is hydroxyl-lower alkyl, a lower alkoxy-lower alkyl group, or a lower alkoxy-lower alkoxy-lower alkyl group.



(I)

The prior art of record is broader in scope because R may represent any protection group, while the instant invention is limited to the group hydroxyl-lower alkyl, a lower alkoxy-lower alkyl group, or a lower alkoxy-lower alkoxy-lower alkyl group.

Resolving Level of Ordinary Skill in the Pertinent Art

The pertinent art is medicinal chemistry, specifically cardiovascular chemistry. On skilled in the pertinent art would be motivated to make and use the instant invention because the R1 groups are known in the relevant art as protective groups for the carboxyl group. The motivation to make

claimed compound derives from the expectation that structurally similar compounds are generally expected to have similar properties and have similar utilities. In re Gyurik, 596 F. 2d 1012, 201 USPQ 552 (CCPA 1979).

Prima Facie Obviousness-The Rational and Motivation (MPEP §2142-2413)

It is well established that consideration of a reference is not limited to the preferred embodiments or working examples, but extends to the entire disclosure for what it fairly teaches, when viewed in light of the admitted knowledge in the art, to a person of ordinary skill in the art. In re Boe, 148 USPQ 507 (CCPA 1966). For an invention to be obvious, two things must be found in the prior art: 1) the suggestion of the invention, and 2) the expectation of success. In re Vaeck, 20 USPQ.2d 1438, 1441 (Fed. Cir. 1991).

The *prima facie* case for obviousness is derived from the preferred teaching of the references. The compound of formula (I) in the prior art of reference is a preferred embodiment.

Also, a stereoisomer is not patentable over its known racemic mixture unless it possesses unexpected properties not possessed by the racemic mixture. *In re Anthony*, 162 USPQ 594, 596 (1969) and *In re Adamson*, 125 USPQ 233, 234 (1960). An optically active isomer is unpatentable over a prior art racemate or optical isomer of opposite rotation in the absence of unexpected or unobvious beneficial properties. *In re Adamson et al.* (CCPA) 1960 275 F2d 952, 125 USPQ 233.

V. **OBJECTION(S)**

Claims 2-12 are objected to because said claims depend from a rejected based claim.

Claim 6 is objected to because claim 6 is a multiple dependent claim and improperly depends from another multiple dependent claim (i.e. claim 4).

VI. CONCLUSION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nyeemah Grazier whose telephone number is (571) 272-8781. The examiner can normally be reached on Monday through Thursday and every other Friday from 8:30 a.m. - 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane, can be reached on (571) 272 - 0699. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Very truly yours,

KAMAL A. SAEED, PH.D.
PRIMARY EXAMINER

Nyeemah Grazier, Esq.
Patent Examiner, Art Unit 1626
UNITED STATES PATENT AND TRADEMARK OFFICE
400 Dulany Street
Alexandria, VA 22314-5774
Tel. No.: (571) 272-8781

Joseph K. McKane
Supervisory Primary Examiner, Art Unit 1626
UNITED STATES PATENT AND TRADEMARK OFFICE
400 Dulany Street
Alexandria, VA 22314-5774
Tel. No.: (571) 272-0699